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DATE: Wednesday, May 14, 2003 Printable Copy Create Case

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DB=USPT,PGPB; PLUR=YES; OP=AND			
L3	l1 and L2	8	L3
L2	(reduc$ or diminish$ or decreas$ or inhibit$) near7 metastas$	3806	L2
L1	aminoalkylphosphorothioate or wr adj (2721 or 1065 or 638 or 77913 or 33278 or 3689 or 2822 or 2529 or 255591 or 2823 or 255709 or 151326 or 151327)	168	L1

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Search Results - Record(s) 1 through 8 of 8 returned.

☐ 1. 20030086924 . 10 Oct 02. 08 May 03. Treatment with anti-ErbB2 antibodies. Sliwkowski, Mark X.. 424/143.1; 424/155.1 A61K039/395.

☐ 2. 20020001587 . 16 Mar 01. 03 Jan 02. Methods of treatment using anti-ErbB antibody-maytansinoid conjugates. Erickson, Sharon, et al. 424/178.1; A61K039/395.

☐ 3. 20010047024 . 21 May 01. 29 Nov 01. Method of using cyclooxygenase-2 inhibitors in the treatment and prevention of neoplasia. Seibert, Karen, et al. 514/406; 514/357 514/365 514/372 514/374 514/438 514/461 A61K031/44 A61K031/415 A61K031/425 A61K031/426 A61K031/42 A61K031/421.

☐ 4. 6469040 . 21 May 01; 22 Oct 02. Method of using cyclooxygenase-2 inhibitors in the treatment and prevention of neoplasia. Seibert; Karen, et al. 514/406; 514/12 514/247 514/254.05 514/271 514/341 514/365 514/372 514/374 514/378 514/399 514/400 514/403 514/407 514/602 514/603 514/604 514/605 514/709 514/8. A61K031/415.

☐ 5. 6217869 . 05 Sep 97; 17 Apr 01. Pretargeting methods and compounds. Meyer; Damon L., et al. 424/178.1; 424/1.53 424/179.1 530/367 530/391.1 530/391.3 530/391.5 530/402. A61K039/00 C07K001/107 C07K016/46.

☐ 6. 6025353 . 19 Nov 97; 15 Feb 00. Method of using cyclooxygenase-2 inhibitors as anti-angiogenic agents. Masferrer; Jaime, et al. 514/210.02; 514/341 514/365 514/372 514/374 514/378 514/399 514/400 514/403 514/406 514/407. A61K043/56.

☐ 7. 6015897 . 13 May 96; 18 Jan 00. Biotinamido-n-methylglycyl-seryl-o-succinamido-benzyl dota. Theodore; Louis J., et al. 540/474;. C07D257/02.

☐ 8. 5972986 . 14 Oct 97; 26 Oct 99. Method of using cyclooxygenase-2 inhibitors in the treatment and prevention of neoplasia. Seibert; Karen, et al. 514/406; 514/247 514/254.05 514/341 514/365 514/372 514/374 514/378 514/399 514/400 514/403 514/407 514/602 514/603 514/604 514/605 514/709. A01N043/56 A61K031/415.

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Terms	Documents
l1 and L2	8

=> d his

(FILE 'HOME' ENTERED AT 19:19:33 ON 14 MAY 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 19:19:48 ON 14 MAY 2003

L1 3229 S AMINOALKYLPHOSPHOROTHIOATE OR WR(W)(2721 OR 1065 OR 638 OR 77
L2 371 S WR(W)(33278 OR 3689 OR 2822 OR 2529 OR 255591 OR 2823 OR 2557
L3 3349 S L1 OR L2
L4 20500 S (REDUC? OR DECREAS? OR DIMINISH? OR INHIBIT?)(7A)METASTAS?
L5 13 S L3 AND L4
L6 6 DUP REM L5 (7 DUPLICATES REMOVED)

=> d bib ab 1-6 l6

L6 ANSWER 1 OF 6 MEDLINE DUPLICATE 1
AN 2002055254 MEDLINE
DN 21634672 PubMed ID: 11774255
TI **Inhibition** of spontaneous **metastases** formation by amifostine.
AU Grdina David J; Kataoka Yasushi; Murley Jeffrey S; Hunter Nancy; Weichselbaum Ralph R; Milas Luka
CS Department of Radiation and Cellular Oncology, University of Chicago, 5841 S. Maryland Ave., Chicago, IL 60637, USA.. dgrdina@rover.uchicago.edu
NC R01 CA 37435 (NCI)
SO INTERNATIONAL JOURNAL OF CANCER, (2002 Jan 10) 97 (2) 135-41. Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200201
ED Entered STN: 20020125
Last Updated on STN: 20020125
Entered Medline: 20020117
AB Amifostine was investigated for its ability to **inhibit** spontaneous **metastases** formation using the well-characterized murine sarcoma, Sa-NH. Amifostine was administered intraperitoneally at a dose of 50 mg/kg every other day for 6 days to C3Hf/Kam mice until tumors reached an average size of 8-8.5 mm in diameter. Amifostine was again administered immediately after surgical removal of the tumor-bearing limbs by amputation, and then once more 2 days later. Twenty-one days later, animals were evaluated for the presence of spontaneously developed pulmonary metastases. Nontumor-bearing control animals were sham treated using the same dosing and surgery schedules. Treatment with amifostine appeared to slightly delay tumor growth, that is, 13 vs. 12 days for tumors to reach an average diameter of 8 mm. Amifostine **reduced** both the incidence of pulmonary **metastases** formed in experimental animals from 77% to 57% ($p < 0.05$), and their average number per animal from 12.8 +/- 5.4 (SEM) to 2.9 +/- 1.1 (SEM). The effect of amifostine exposure on serum levels of the angiogenesis inhibitor angiostatin was also determined using Western blot analysis. Consistent with the antimetastatic effect, exposure of animals to 50 mg/kg of amifostine resulted in a 4-fold enhanced serum level of angiostatin above control levels. This phenomenon occurred in tumor-bearing and nontumor-bearing animals. The effects of amifostine on matrix metalloproteinase (MMP) enzymatic activity was also determined using gelatin zymography. Conditioned growth medium collected from Sa-NH cells grown to confluency was exposed to various concentrations of SH, i.e., 2-[(aminopropyl)amino]ethane-thiol (**WR-1065**), the active thiol form of amifostine, for either 30 min or 18 hr. **WR-1065**, as a function of increasing dose and time, inhibited the enzymatic activities of MMP-2 and MMP-9. At a concentration and time of

exposure likely to be achieved in vivo, that is, 40 microM and 30 min, MMP-2 and MMP-9 activities were reduced to between 30% and 40% of control values. Consistent with these affects, **WR-1065** was also found to be effective in inhibiting the ability of Sa-NH cells to migrate through Matrigel membranes. After an 18-hr exposure under in vitro conditions, **WR-1065** at concentrations of 4, 40 and 400 microM, and 4 mM, inhibited Sa-NH migration to 11%, 44%, 81% and 97% of control values, respectively. The abilities of amifostine and its active thiol **WR-1065** to stimulate angiostatin production in mice, and to inhibit the MMP enzymatic activities and invasion ability of Sa-NH cells under in vitro conditions, are consistent with the observed antimetastatic effects exhibited against Sa-NH tumors growing in vivo.

L6 ANSWER 2 OF 6 CAPLUS

AN 2001:881484 CAPLUS
DN 136:177611

TI A phase II trial of cisplatin plus **WR-2721** (amifostine) for metastatic breast carcinoma: An Eastern Cooperative Oncology Group study (E8188)

AU Gradishar, William J.; Stephenson, Patricia; Glover, Donna J.; Neuberg, Donna S.; Moore, Melvin R.; Windschitl, Harold E.; Piel, Ira; Abeloff, Martin D.

CS Northwestern University Medical School, Chicago, IL, 60611, USA

SO Cancer (New York, NY, United States) (2001), 92(10), 2517-2522
CODEN: CANCAR; ISSN: 0008-543X

PB John Wiley & Sons, Inc.

DT Journal

LA English

AB BACKGROUND. Cisplatin has minimal antitumor activity when used as second- or third-line treatment of metastatic breast carcinoma. Older reports suggest an objective response rate of 8% when 60-120 mg/M2 of cisplatin is administered every 3-4 wk. Although a dose-response effect has been obsd. with cisplatin, the dose-limiting toxicities assocd. with cisplatin (e.g., nephrotoxicity, ototoxicity, and neurotoxicity) have limited its use as a treatment for breast carcinoma. **WR-2721** or amifostine initially was developed to protect military personnel in the event of nuclear war. Amifostine subsequently was shown to protect normal tissues from the toxic effects of alkylating agents and cisplatin without decreasing the antitumor effect of the chemotherapy. Early trials of cisplatin and amifostine also suggested that the incidence and severity of cisplatin-induced nephrotoxicity, ototoxicity, and neuropathy were reduced. METHODS. A Phase II study of the combination of cisplatin plus amifostine was conducted in patients with progressive metastatic breast carcinoma who had received one, but not more than one, chemotherapy regimen for metastatic disease. Patients received amifostine, 910 mg/M2 i.v. over 15 min. After completion of the amifostine infusion, cisplatin 120 mg/M2 was administered over 30 min. I.v. hydration and mannitol was administered before and after cisplatin. Treatment was administered every 3 wk until disease progression. RESULTS. Forty-four patients were enrolled in the study of which 7 (16%) were ineligible. A median of 2 cycles of therapy was administered to the 37 eligible patients. Six partial responses were obsd. for an overall response rate of 16%. Most patients (57%) stopped treatment because of disease progression. Neurol. toxicity was reported in 52% of patients. Seven different life-threatening toxicities were obsd. in patients while receiving treatment. CONCLUSIONS. The combination of cisplatin and amifostine in this study resulted in an overall response rate of 16%. Neither a tumor-protective effect nor reduced toxicity to normal tissues was obsd. with the addn. of amifostine to cisplatin in this trial.

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 2000:688056 CAPLUS
DN 133:247270
TI Phosphorothioates and phosphorothioate metabolites for protection against tumor metastasis formation
IN Grdina, David J.; Milas, Luka
PA Arch Development Corp., USA; Board of Regents, the University of Texas System
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056299	A2	20000928	WO 2000-US6653	20000314
WO 2000056299	A3	20010118		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-125605P P 19990319
US 2000-523886 A1 20000313

AB Methods and pharmaceuticals are provided for **inhibiting** or preventing **metastasis** formation in animals, including humans, having primary tumors, through the administration of phosphorothioates including their thiol and disulfide metabolites. These compds. stimulate angiostatin levels, inhibit matrix metalloproteinases, and stimulate manganese superoxide dismutase. Phosphorothioates, e.g. amifostine, can be administered as a combination therapy with traditional cancer therapies, including chemotherapy, radiotherapy, surgery, immunotherapy, hormone therapy, and gene therapy. **Inhibition** or prevention of **metastasis** by phosphorothioates is independent of tumor type, including adenocarcinomas and sarcomas.

L6 ANSWER 4 OF 6 MEDLINE DUPLICATE 2
AN 84205376 MEDLINE
DN 84205376 PubMed ID: 6327014
TI Protection by S-2-(3-aminopropylamino)ethylphosphorothioic acid against radiation- and cyclophosphamide-induced attenuation in antitumor resistance.
AU Milas L; McBride W H; Hunter N; Ito H
NC CA-06294 (NCI)
CA-16672 (NCI)
SO CANCER RESEARCH, (1984 Jun) 44 (6) 2382-6.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198407
ED Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840712
AB Studies were performed to investigate whether S-2-(3-amino-propylamino)ethylphosphorothioic acid (**WR-2721**) can protect antitumor immune rejection responses against the damaging effects of whole-body irradiation (WBI) and cyclophosphamide (CY). Among these damaging effects were radiation-induced enhancement of s.c. tumor take and

radiation- and CY-induced enhancement of lung colonization by tumor cells injected i.v. The ability of **WR-2721** to protect against WBI -induced decreased radioresponse of solitary tumors was also investigated. All experiments were performed with an immunogenic fibrosarcoma syngeneic to C3Hf/ Kam mice. **WR-2721** was given i.p. at a dose of 400 mg/kg 30 min before WBI with gamma-rays or CY injection. WBI with 650 rads reduced the number of tumor cells needed for tumor take in 50% of animals from 5.1 X 10(4) cells in normal mice to 2.0 X 10(2). **WR-2721** given before WBI almost entirely abolished the effect of WBI : the number of tumor cells needed for tumor take in 50% of animals was 1.4 X 10(4). Treatment of mice with WBI or CY increased the number of tumor nodules in the lung generated by fibrosarcoma cells injected i.v. 5 days later, in a linear dose response. **WR-2721** greatly **reduced** this **metastasis** enhancement effect of WBI and CY with protection factors of 2.5 for WBI and 1.8 for CY. Fibrosarcomas of 8 mm in diameter exhibited a decreased radiocurability when growing in WBI mice: the dose of irradiation yielding local tumor control in 50% of animals in these mice was 5950 compared to a dose of irradiation yielding local tumor control in 50% of animals of 4160 rads in normal mice. **WR-2721** given before WBI inhibited this effect of WBI : the dose of irradiation yielding local tumor control in 50% of animals was 5210 rads. The proportion of macrophages in tumors growing in WBI mice was significantly reduced, but not when **WR-2721** was first given. **WR-2721** greatly reduced the damaging effects of WBI and CY on natural killer cell activity. Therefore, **WR-2721** was capable of protecting the immune mechanisms involved in antitumor resistance against WBI and CY. This might be of therapeutic benefit when **WR-2721** is combined with radio- or chemotherapy.

L6 ANSWER 5 OF 6 MEDLINE DUPLICATE 3
AN 83206571 MEDLINE
DN 83206571 PubMed ID: 6303574
TI Effect of tumor size on S-2-(3-aminopropylamino)ethylphosphorothioic acid and misonidazole alteration of tumor response to cyclophosphamide.
AU Milas L; Ito H; Hunter N
NC CA-06294 (NCI)
SO CANCER RESEARCH, (1983 Jul) 43 (7) 3050-6.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198307
ED Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19830729
AB The influence of tumor size on the ability of S-2-(3-aminopropylamino)ethylphosphorothioic acid (**WR-2721**) or misonidazole (MISO) to alter cyclophosphamide (CY) antitumor activity was investigated, using a chemically induced fibrosarcoma (FSA) and a spontaneous fibrosarcoma (NFSA) in C3Hf/Kam mice. Tumors were of two sizes at the time of treatment, 8-mm leg tumors and 4-day-old micrometastases in the lung. The antitumor activity of CY and its modification were assessed by growth delay of leg tumors and the **reduction** in the number of lung **metastases**. Both measures of tumor response were more pronounced as the dose of CY increased, and FSA was more sensitive to CY than was NFSA. **WR-2721** (400 mg/kg), given 30 min before treatment with CY, reduced the effectiveness of CY on both FSA and NFSA. This reduction in effectiveness of CY was only minimal for leg tumors (dose-modifying factors were 1.1 for FSA and 1.03 for NFSA) but remarkable for lung micrometastases (dose-modifying factors were 1.81 for FSA and 1.55 for

NFSA). Protection increased with the increase in the dose of **WR-2721** and was also dependent on the time of injection relative to CY. The greatest protection occurred when **WR-2721** was given within 30 min before to 15 min after CY. Tumor size had the opposite effect on MISO from that on **WR-2721**. MISO (1 mg/g) enhanced the effect of CY more effectively for leg tumors than for lung micrometastases: dose-modifying factors were 1.74 for FSA and 2.21 for NFSA growing in the leg and 1.27 for FSA and 1.11 for NFSA lung micrometastases. Therefore, tumor size appears to be a very important factor in determining the extent of **WR-2721**- and MISO-induced modification of CY antitumor effect.

L6 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 1976:441016 CAPLUS
DN 85:41016
TI Influence of **WR-2721** on metastatic tumor spread after irradiation
AU Ullrich, R. L.; Jernigan, M. C.; Yuhas, J. M.
CS Oak Ridge Natl. Lab., Oak Ridge, TN, USA
SO Report (1975), CONF-751001-1, 4 pp. Avail.: NTIS
From: ERDA Res. Abstr. 1976, 1(1), Abstr. No. 00686
DT Report
LA English
AB The Line 1 alveolar cell carcinoma is a transplantable murine tumor which, unlike most others, kills the host by means of metastatic spread. Attempts to cure this tumor with localized radiation therapy often fail, in spite of local tumor control, because the metastases evade the treatment. These facts suggest that host-tumor interactions may play a particularly important role in detg. the ultimate survival of the tumor bearing animal. In order to initially evaluate the possible importance of normal regional tissues in host-tumor interactions the influence of **WR-2721** [20537-88-6], a radioprotective drug, was examd. for local tumor control and subsequent survival of the tumor bearing animal after localized radiation. Results indicated that **WR-2721** can **decrease metastasis**.

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